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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/805,881	03/22/2004	Ibert C. Wells	800812-0005	9725

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EXAMINER

SZPERKA, MICHAEL EDWARD

ART UNIT	PAPER NUMBER
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1644

DATE MAILED: 12/16/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/805,881

Applicant(s)

WELLS, IBERT C.

Examiner

Michael Szperka

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1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 11 October 2005.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,3-6,19 and 31-40 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,3-6,19 and 31-40 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>11/14/05</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 11, 2005 has been entered.

Applicant's response and amendments received October 11, 2005 are acknowledged.

Claims 1, 3, and 19 have been amended.

Claims 31-40 have been added.

Claims 1, 3-6, 19, and 31-40 are pending and under consideration in this office action.

Information Disclosure Statement

2. Applicant's IDS received November 14, 2005 is acknowledged and has been considered.

Claim Objections

3. Claims 1, 3, 19, 31, 32, 36, and 37 are objected to because they lack an article appearing ahead of the recitation "amino acid sequence set forth in SEQ ID NO:x."

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Addition of the article "the" would place the claims more in accord with standard grammar, would indicate that the recited peptide consists of only exactly the peptide of SEQ ID NO:x such that the claim cannot be said to read upon fragments that are found wholly within said SEQ ID number (as would occur if the indefinite article "a" or "an" were to be used), and presumably would not alter applicant's intended scope of the claim.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1, 3-6, and 19 stand rejected and new claims 31-40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention for the reasons of record set forth in the Office action mailed April 8, 2005.

Applicant's arguments filed October 11, 2005 have been fully considered but they are not fully persuasive. Applicant argues that the specification does provide evidence for a correlation between the level of Peptides (term used by applicant to collectively refer to the peptides consisting of SEQ ID NOs:1, 2, and 4) and the magnesium binding defect (MgBD). Applicant further argues that the specification teaches in example 4 that

women diagnosed with preeclampsia also have MgBD as determined by measuring Mg bound to erythrocyte membranes. Applicant then argues the conclusion that since Peptides correlate with MgBD, and MgBD correlates with preeclampsia, then Peptides must correlate with preeclampsia.

This is not convincing for the reasons of record, namely that applicant has not shown a direct link between the detection of Peptides and the detection of preeclampsia. Applicant is correct in the statement that the specification teaches that the administration of Peptides to rats *in vivo* corrected hypertension and MgBD, and that *in vitro* incubation of Peptides with human erythrocytes increased Mg binding to the plasma membrane (see particularly paragraph 47, Examples 2, 3 and 7). However, support for applicant's statement in the middle of the first paragraph of page 10 of the reply indicating that the measured plasma level of Peptides was decreased in a rat model of MgBD as compared to the measured value in controls could not be located in Example 2 or paragraph 47, and applicant is invited to clearly point out where support for this statement can be found. As such, it while administration of peptides may reverse MgBD, it is not clear that detection of lower than normal levels of Peptides is causative of MgBD or is predictive of the presence of MgBD. In the absence of such evidence, applicant's chain of associative reasoning fails, and one cannot reasonably conclude that the detection of Peptides correlates with preeclampsia. Further, as was noted in the rejection of record, neither the detection of Peptides nor the detection of MgBD is an art recognized method for diagnosing preeclampsia as taught by Merck.

Applicant also argues that the teachings of Page et al. discussed in the rejection of record are not relevant because they address the full length polypeptide of NKB and not the breakdown products of NKB (the genus of which reasonable includes the polypeptides consisting of SEQ ID NO:2 and 4). The rejection or record acknowledges applicant's point, but it is not clear to the examiner how if the concentration of a precursor sequence increases (i.e. NKB), the concentration of its breakdown products (i.e. SEQ ID NO:2, 4) decreases, and applicant is still invited to address this issue.

The instant claims also indicate that the recited method detect a predisposition in an individual that places them at risk for developing preeclampsia. Applicant's arguments concerning this issue are not persuasive. First, applicant's amendment has removed references to pregnancy in an attempt to clarify the intended patient population. However, this amendment appears to remove the indication that the claimed method be performed on female patients, and since males cannot have preeclampsia the instant method claims do not appear to be enabled for about 50% of the human population. Second, applicant argues that the examiner is unreasonable in the statement that predisposition indicates that something (in the instant case, preeclampsia) is more likely than not to happen at a future date. Applicant has provided dictionary references that define predisposition as "tendency, inclination or susceptibility" and "a condition of special susceptibility, as to a disease." In order for a tendency, inclination, or susceptibility to be observed in a patient population that item must occur more often than what would be expected to occur due to random chance in said patient population. In the instant case, this would mean that detection of Peptides

in a woman means that the woman is more likely to develop preeclampsia than what would be predicted to happen due to random chance. If an outcome is more likely than not to occur, it is occurring at a frequency greater than that which would be expected by random chance. As such, the examiner's statement in the rejection of record is in accord with the definitions entered by applicant and with the connotations of what this term means to a skilled artisan. Further, if variables are truly correlated, (such as Peptide level and risk of preeclampsia) then observation of one variable would make it more likely than not that the other variable will be detected. As was stated in the rejection of record, the specification does not provide evidence that measuring Peptides in a female patient has predictive power in selecting those individuals that will develop preeclampsia, and as such no predisposition to developing preeclampsia can be detected by performing applicant's claimed methods. For all of the above discussed reasons the rejection is maintained.

6. Claim 19 stands rejected and new claims 31-35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of measuring peptides consisting of SEQ ID NO:1 or SEQ ID NO:4, does not reasonably provide enablement for methods of measuring peptides consisting of SEQ ID NO:2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims for the reasons or record set forth in the office action mailed April 8, 2005.

Applicant's arguments filed October 11, 2005 have been fully considered but they are not persuasive. Applicant has argued that only routine experimentation would be required to generate an antibody that binds to a peptide consisting of SEQ ID NO:2. SEQ ID NO:2 is a tetrapeptide that is completely contained within the larger pentapeptide of SEQ ID NO:1. SEQ ID NO:4 is degenerate pentapeptide that contains SEQ ID NO:1 and the sequence FVGLM. Applicant argues that it was recognized in the art that epitopes are often comprised of only 4 or 5 amino acids, and that only routine screening would be required to find an antibody that had the ability to bind to a tetrapeptide consisting of SEQ ID NO:2. The examiner agrees that antibodies may be able to bind a linear peptide epitope that consists only of four amino acids, and as such tetrapeptides can be *antigenic*. However, Harlow et al. teach that the smallest synthetic peptide that will consistently elicit antibody responses (and hence is *immunogenic*) is 6 amino acids in length, with approximately 10 amino acids being preferred as the lower limit for the production of antibodies (see Harlow et al., *Antibodies, A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988, cited by applicant on page 15, paragraph 46 of the instant specification, specifically Chapter 5, page 76). As such, the generation of an antibody that binds an epitope of 4 amino acids is not considered a routine procedure that is generally performed in the art. As has been stated in the rejections of record, Couraud et al. (*J Neurochem*, 1987, 49:1708-1719, of record, see entire document) performed standard, art recognized procedures described by Harlow et al. in generating their antibodies. Specifically, they teach polyclonal and monoclonal antibodies that were generated using the 11 amino acid neuropeptide substance P

(SP), and they mapped the binding of these reagents to smaller polypeptide sequences. Their data indicated that while antibodies that bind a pentapeptide consisting of SEQ ID NO:1 were readily observed (the polyclonal serum and 5 out of 5 distinct monoclonal antibodies), no reactivity was observed to the tetrapeptide consisting of SEQ ID NO:2. The lack of binding in the polyclonal serum is particularly noteworthy, since it indicates that antibodies with the requisite binding specificity are not readily generated.

Given that the application does not disclose a working example that uses antibodies that bind the polypeptide sequence of SEQ ID NO:2, that antibodies that bind some but not all SP fragments (one of which includes the peptide of SEQ ID NO:1) as taught by Couraud et al. were generated using standard, art recognized techniques, that while it is known that antibodies can bind small linear peptides, such as a peptide consisting of 4 amino acids, it is not routine to generate antibodies using such small sequences as an immunogen as taught by Harlow et al., and since the specification does not indicate that anything other than standard art recognized procedures are required to make an antibody that binds a tetrapeptide consisting of SEQ ID NO:2, it does not appear that a skilled artisan would be able to make and use the full breadth of applicant's claimed invention, especially in the absence of evidence to the contrary. Therefore the rejection of record is maintained.

New Grounds of Rejection

The following new ground of rejection is necessitated by Applicant's amendment to the claims received October 11, 2005.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 5 and 34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, claim 5 recites that a monoclonal antibody cross reacts with each of said peptides, yet the only peptide in the base claim is SEQ ID NO:1. SEQ ID NO:1 is defined as the sequence FFGLM, and as such there is only one peptide present. The situation with claim 34 is analogous. Deleting claims 5 and 34 is one way to overcome this rejection.

9. No claims are allowable.


10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Szperka whose telephone number is 571-272-2934. The examiner can normally be reached on M-F 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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December 5, 2005


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12/7/05